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HEAD AND NECK CANCERS (EY HANNA, SECTION EDITOR)

Cutaneous Squamous Cell Carcinoma in Immunosuppressed Patients

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Abstract

Purpose of Review Cutaneous squamous cell carcinoma is the second most common dermatologic malignancy worldwide. A major risk factor for development of new lesions and more aggressive disease is immunosuppression. This study is aimed at summarizing the current knowledge of the treatment of cutaneous squamous cell carcinoma of the head and neck (cSCCHN) in immunosuppressed patients.

Recent Findings As the variety of pharmaceutical alternatives for immunosuppression expands, the application of immunosuppression has increased. As the population at risk for cSCCHN due to immunosuppression has increased, our understanding of link between immunosuppression and cancer has expanded. In addition to surgery, adjuvant radiotherapy and systemic therapy remain major players in high-risk patients with cSCCHN. While immunotherapy demonstrates promise in immunocompetent cSCCHN patients, its role in immunosuppressed patients still needs to be delineated.

Summary Immunosuppressed patients are at higher risk of developing synchronous cSCCHN, each with an increased risk of recurrence. While surgery remains mainstay of treatment, further understanding is required to delineate the evolving role of adjuvant and potentially neoadjuvant therapies.

Keywords Cutaneous · Squamous cell carcinoma · Immunosuppression · Head and neck

Introduction

Nonmelanomatous skin cancer is the most common cancer worldwide. Squamous cell carcinoma represents the second most common type of skin malignancy, after basal cell carcinoma, and represents approximately 20% of all skin malignancies [1]. There are approximately 700,000 new cases of cutaneous squamous cell carcinoma (cSCC) per year in the USA [2••]. The most common site of cSCC is the head and neck, and treatment can be especially challenging due to cosmetic and functional concerns [3].

While treatment of cSCC of the head and neck (cSCCHN) is often adequate with surgical excision, there is a subset of disease that is more aggressive, requiring more extensive surgical resection and potential adjuvant treatment. The National Comprehensive Cancer Network (NCCN) guidelines outline high-risk features, which includes pathologic and patient factors, such as immunosuppresssion [4]. Immunosuppressed patients are at a 65- to 100-fold increased risk of developing cSCC [5]. While the incidence of basal cell carcinoma is 4:1 in the immunocompetent population, this ratio is reversed in the immunosuppressed population, with cSCC 4 times more common than basal cell carcinoma [6]. Notably, the risk of cSCCHN is estimated to increase by 5% annually after solid organ transplantation [7]. This review is aimed at summarizing the current knowledge about the epidemiology, outcomes, and treatment options in immunosuppressed patients with cSCCHN.

Defining Immunosuppression

When considering the epidemiology of cSCCHN in immunosuppressed patients, definitions of immunosuppression vary according to the cohort studied. Organ transplant patients are known to be at an increased risk of cSCCHN. Organ transplant recipients are 65–100 times more likely to develop cSCC compared with the general population [8]. Within

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10 years of transplantation, 30% of patients with transplants have cSCC, and, within 20 years, 70% are affected [9]. As well, in patients that have developed a nonmelanomatous skin cancer, 75% develop another within the next 5 years [10]. It is not uncommon for immunosuppressed patients with cSCC to develop innumerable skin malignancies and premalignancies (Fig. 1).

The risk of cancer in patients undergoing organ transplant is proportional to the amount of immunosuppressive therapy required. As such, patients with heart transplants are at a greater risk than lung transplant patients, who are at a greater risk than renal transplant patients [6]. In addition, administration of voriconazole, an antifungal used prophylactically in patients with lung transplantation, may further increase the risk of cSCC. In one study, voriconazole use resulted in a 73% increased risk of cSCC among patients with lung transplants [11]. This effect has also been demonstrated in patients undergoing a hematopoietic stem cell transplant [12]. However, despite this increase in incidence of cSCC, there is no effect of voriconazole use on mortality [11]. This is likely because voriconazole is an effective prophylactic for aspergillus infection, and the increased risk of cSCCHN is counteracted by the decreased mortality of opportunistic pneumonia.

In patients with organ transplantation, race is a major predictor of risk of cSCC [5]. In a study of 259 non-Caucasian patients with organ transplantation, only 5.8% had a nonmelanomatous skin cancer or premalignancy. Of these patients, only one had a cSCC. Thirteen patients had cSCC in situ, which may reflect the increased screening of these patients in this prospective cohort study. cSCC most usually presents in sun-exposed areas in the Caucasian population. Though this is mirrored in the Asian population in this cohort, all lesions in the African-American population were found in sun-protected areas. Therefore, though the risk of cSCC still exists in non-Caucasian organ transplant patients, their pattern of presentation differs widely.

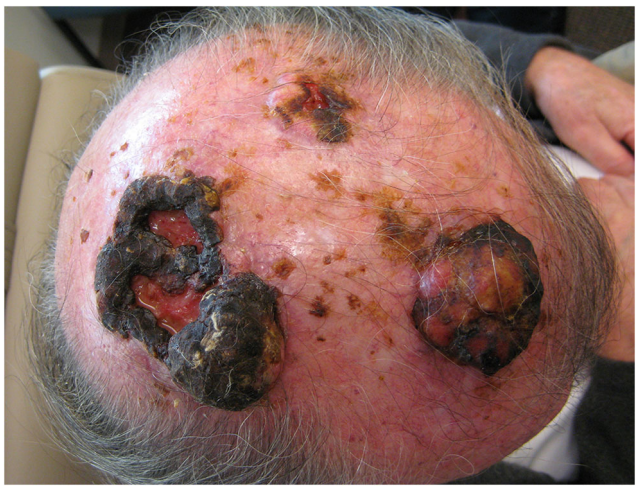

Fig. 1 Patient with immunosuppression demonstrating multifocal, aggressive cutaneous squamous cell carcinoma of the scalp

Another source of immunosuppression is in patients with hematopoietic malignancies. Patients with chronic lymphocytic lymphoma (CLL) have an 8–10 times risk of developing cSCC compared with the general population [8]. Hematopoietic malignancies result in immunosuppression due to the disease itself, but also treatment for the disease. For example, CLL causes downregulation of CD40 ligand on T lymphocytes and increases levels of IL-2. This results in poorer antibody production resulting in a dampened immune response and increased susceptibility to malignancy [13]. In addition, agents used to treat CLL may also result in immunosuppression, though there does not exist clear evidence of a correlation between treatment using alkylating agents or nucleoside analogs and cSCC [13]. In patients with multiple myeloma treated with immunomodulating agents, there is a 2.44 times increased incidence of cSCC compared with patients without multiple myeloma [14]. Lastly, in patients with chronic lymphocytic leukemia, high-stage leukemia staging was found to be an independent predictor of worse cSCC-specific disease-free survival [15].

While organ transplantation and hematopoietic malignancies are the most commonly investigated causes of immunosuppression in patients with cSCC, other causes of immunosuppression are important to consider. In patients with autoimmune disease, there is an observed increased in incidence of cSCC. In patients with rheumatoid arthritis, treatment with tumor necrosis factor (TNF) alpha inhibitors demonstrated a 1.5 times increased risk of nonmelanomatous skin cancer [16]. There was also observed an increased risk with NSAID or glucocorticoid steroid use, but to a lesser degree [17]. TNF alpha inhibitors have also been demonstrated to increase risk of cSCC in patients with psoriasis [18]. In 5,889 patients treated systemically for psoriasis, those using biologic agents were 86% more likely to have a diagnosis of cSCC compared with those without biologic use [18]. Among biologics, TNF alpha was the most common agent. Thiopurine use has also been demonstrated to increase the risk of nonmelanomatous skin cancer in patients with inflammatory bowel disorders and psoriasis [19].

Atopic dermatitis is another autoimmune disease for which systemic immunosuppressant therapy is used for disease control. Atopic dermatitis patients on immunosuppressive medications demonstrated an 8.8 times increased incidence of cSCC compared with the general population [19]. This was especially high in patients undergoing monotherapy with cyclosporine A, who had a 25.3 times increased incidence of cSCC compared with the general population. Unfortunately, the control population was derived from a cancer registry without further details of important risk factors for cSCC such as ultraviolet radiation exposure and Fitzpatrick score.

Human immunodeficiency virus (HIV) is major reason for immunosuppression. While cSCC is not considered an acquired immunodeficiency syndrome (AIDS)-defining malignancy, cSCC is the second most common non-AIDS-defining malignancy and is present in 12% in a cohort of 133 patients with any non-AIDS-defining malignancy [20]. As well, in a large cohort study involving 6,560 HIV positive patients, patients with HIV were found to have a 2.6 times increased incidence rate of cSCC compared with HIV negative subjects [21].

While diabetes mellitus is an immunosuppressive condition, the best data available does not demonstrate a link between diabetes and cSCC. Large longitudinal cohort studies did not demonstrate any increased risk of cSCC in patients with type 2 diabetes [22]. It should be noted, however, that this study did not stratify according to the severity of disease.

Prognosis

Primary Disease

Patients with a history of immunosuppression not only develop cSCC more frequently, but the skin cancers they develop behave more aggressively. In organ transplant recipients, skin cancers grow faster, have a higher propensity for distant and regional metastasis, and demonstrate more adverse pathologic features [6, 9]. Immunosuppressed patients with cSCCHN treated with surgery and radiation have a higher proportion of poorly differentiated disease compared with the immunocompetent patients [2••]. Immunosuppressed patients with cSCCHN show an increased rate of lymphovascular invasion and extracapsular extension compared with immunocompetent patients [23]. Additionally, immunosuppressed patients were also found to have increased early dermal invasion, have more infiltrative changes, and have thicker primary tumors [24]. Immunosuppressed patients have also been found to have more frequent multifocal disease, more likely to demonstrate discontinuous spread or satellitosis, resulting in recurrences even far away from the primary disease site [6, 10]. As well, immunosuppressed patients are more likely to present with nodal disease at the time of presentation [4].

Recurrent Disease

Manyam et al. studied a cohort of 205 patients, with 138 (67.3%) patients were immunocompetent and 67 (33%) patients were immunosuppressed [2••]. In this cohort, 54% of immunosuppressed patients experienced locoregional recurrence, compared with 17% of immunocompetent patients ($p < 0.001$). Among immunosuppressed patients with cSCCHN, locoregional failure is the most common pattern of failure (47%), followed by local recurrence (45%) [2••]. The rate of distant metastatic disease was not different between the two groups. Two-year locoregional recurrence free survival rate was worse for immunosuppressed patients (38.7%) compared with immunocompetent patients (86%, $p < 0.001$). This difference did not translate into a difference in overall survival between the two groups. In this cohort, immunosuppression continues to be a predictor of locoregional recurrence after adjusting for recurrence status, tumor cell differentiation, and presence of perineural invasion [2••].

Varra et al. confirmed the importance of immunosuppression in patients with cSCCHN using a cohort of 76 patients with known nodal disease at baseline. Comparing 57 (75%) immunocompetent patients with 19 (25%) immunosuppressed patients, immunosuppression was found to be an independent predictor of poor disease-free survival, after controlling for prior receipt of chemotherapy [25]. In another study, immunosuppressed patients were found to have a 1.6 times increased risk of regionally or distantly metastatic disease [19]. Unfortunately, once an immunosuppressed patient has experience regional recurrence of their disease, prognosis was poor, advocating for aggressive treatment in this cohort [26••].

Due to the aggressiveness, persistence, and relapsing nature of the disease, cSCC is the major cause of mortality in heart transplant patients. In these patients, approximately 27% of deaths can be attributable to skin cancer [13].

Treatment Options

Studies focusing on treatment of cSCC in immunosuppressed patients are lacking (Table 1). However, principles of treatment derived from studies focusing on immunocompetent patients guide treatment recommendations in immunosuppressed patients.

Prevention

Primary prevention by decreasing exposure of risk factors is the most effective method of decreasing cSCCHN in immunosuppressed patients. In all patients with risk factors of cSCC, and furthermore in immunosuppressed patients, sun protection should become a regular part of life. In patients with organ transplantation, 90% of cSCC presents in sun-exposed areas [6]. Thus, all clinical guidelines suggest avoidance of sunburn, intentional tanning, or unnecessary ultraviolet exposure [6, 33]. In addition, high-SPF, broad-spectrum sunscreen and sun-protective clothing is necessary.

Despite the emphasis on preventative techniques for cSCC in clinical guidelines, patient education is lacking [34]. Despite a standard posttransplant skin education program, only 66% of patients recalled having received advice about sun

Table 1 Studies investigating treatment for cutaneous squamous cell carcinoma in immunosuppressed patients

Author	Type of study	Cohort included	Treatment	Summary of results
Bavinck et al. [27]	Randomized controlled trial	44 patients with renal transplantation	Acitretin30 mg daily × 6 months vs. placebo	Decreased occurrence of cSCC but poor duration of response
Euvarad et al. [28]	Randomized controlled trial	100 patients with renal transplantation	Sirolimus vs. carcineurin inhibitor	HR 0.37 (95% CI = 0.16–0.85) cSCC-free survival of sirolimus group compared with a calcineurin inhibitor group
Jirakulaporn et al. [29]	Retrospective case series	15 patients with solid organ transplantation	Oral capecitabine 1 g/m^2 BID × 14 days	Following treatment, incidence of lesions decreased by 0.33 times
Ulrich et al. [30]	Randomized controlled trial	43 patients with renal, liver, and heart transplantation	Topical imiquimod 3×/week vs. placebo	62% clearance of actinic keratosis with topical imiquimod vs. 0% with placebo
Ulrich et al. [31]	Randomized controlled study	32 patients with solid organ transplantation	Topical diclofenac vs. placebo	42% complete clearance of actinic keratosis vs. 0% in placebo
Willey et al. [32]	Prospective case series	12 patients with solid organ transplantation	Cyclic photodynamic therapy	79% reduction in cSCC and cSCC in situ at 12 months and 95% at 24 months

protection following liver transplant surgery and only 48% of patients recall being told about the increased risk of skin cancer. Though 78% used sun protection and 66% patients used sunscreen, 68% of those used sunscreens with sun SPF ratings lower than recommended. With the high incidence of cSCCHN in transplant populations and the relative ease of proper sun protection, frequent education from all providers involved in the care of immunosuppressed patients may improve adherence.

Systemic retinoids have been investigated in patients with multiple (5–10/year) cSCC [13]. Retinoids have demonstrated an effect on premalignant lesions. In a randomized, phase II clinical trial of systemic retinoids in 39 patients with renal transplantation, patient treated with retinoids demonstrated a decreased incidence of cSCC [27]. This effect was greatest in patients with a history of skin cancer. However, the duration of the response was limited. Following discontinuation of systemic retinoids, many patients had a relapse of lesions. The lack of duration of response, as well as possible side effects from long-term treatment with systemic retinoids, has limited the broad acceptance of this treatment.

Capecitabine, an oral prodrug of 5-fluorouracil, has also been investigated in patients with organ transplants [29]. In a small study, capecitabine was found to decrease the incidence of cSCC and premalignancies during immunosuppressive treatment after solid organ transplant. As well, the side effect profile was much more tolerable, with a median treatment time of 12.9 years, demonstrating greater promise of this treatment for immunosuppressed patients.

Changing Immunosuppressive Regimens

A major component in the development of cSCC in patients with organ transplantation is the amount and type of immunosuppressive medications used to prevent graft failure. Calcineurin inhibitors such as cyclosporine or tacrolimus have been noted to increase the risk of cSCC in multiple studies [13, 35•].. On the other hand, there has been in increased interest in inhibitors of the mammalian target of rapamycin (mTOR) for both its immunosuppressive and antineoplastic properties. In a randomized controlled trial comparing sirolimus (an mTOR inhibitor) vs. calcineurin inhibitor in 120 patients with renal transplantation [28] at 2 years, patients on sirolimus had a longer cSCC-free survival. During this time, there were also no observed graft rejection events. Thus, mTOR inhibitors represent a good immunosuppressive alternative that is effective in preventing graft failure while also minimizing the risk for developing new cSCC.

Treatment of Premalignant Lesions

Because of the aggressive nature of skin cancers in immunosuppressed patients, aggressive treatment of premalignant lesions is warranted. As such, the threshold to biopsy a lesion

should be low. Moioli et al. completed a histologic analysis of 129 patients with biopsy proven cSCC in situ [36]. Of these, 30 patients were immunosuppressed and nearly half of these demonstrated residual disease after biopsy. As well, 6% of patients demonstrated invasive cSCC at the time of excision. Thus, attention should be paid to immunosuppressed patients with cSCC in situ as close biopsy alone may be not adequate treatment and biopsy may not be representative of the true extent of the tumor.

Local destructive techniques can be considered in actinic keratosis. For localized disease, electrocautery and curettage can be considered. As well, topical imiquimod has demonstrated a 62% rate of clearance of premalignant lesions, and topical diclofenac a 41% rate of clearance in immunosuppressed patients [30, 31]. For larger areas, photodynamic therapy can clear an area of premalignant lesions. Following 1 or 2 treatments of photodynamic therapy, there is clearance of premalignant lesions for up to 3 months in patients with organ transplants [32, 37].

Ingenol mebutate is the active agent in *Euphorbia peplus*, a novel agent used to treat actinic keratosis. A randomized controlled trial was recently conducted using ingenol mebutate in 547 patients with premalignant lesions in the head and neck [38]. In this study, 42% of patients had complete clearance of their lesions in the treatment group, compared with 4% in the control group. At 12 months, there was a 46% rate of sustained clearance of actinic keratosis [39]. While the safety and efficacy of this has not been tested in immunosuppressed patients, the results demonstrated in immunocompetent patients demonstrate promise.

Treatment of Primary Tumors

Surgical excision is the treatment of choice for patients with cSCC. In the head and neck especially, cosmetic and functional concerns need to be considered. As such, Mohs micrographic surgery may be considered for well-delineated, early-stage cSCC for optimal tissue conservation. However, due to the aggressive nature of cSCC, wide local excision should also considered when appropriate [13]. It must be noted that patients with immunosuppression secondary to lymphoproliferative disease may have obscured margins, making Mohs micrographic surgery more challenging. In a cohort of 168 patients undergoing Mohs micrographic surgery, 55 patients had chronic lymphocytic lymphoma and 8 had organ transplantation [40]. Patients with lymphoma were statistically significantly more likely to have dense lymphocytic infiltrates in the tumors. Importantly, in patients with lymphoma, there was a higher rate of subclinical tumor extension to the margin compared with patients with organ transplantation and immunocompetent patients.

According to the NCCN guidelines, the presence of clinical or radiographic nodal disease necessitates neck dissection [41]. Usually, clinically and radiographically negative regional nodal basins undergo active surveillance. However, in high-risk patients, including those with immunosuppression, elective neck dissection or sentinel lymph node biopsy can be used for risk stratification [6].

Radiation Therapy

Radiation therapy as primary treatment of cSCCHN has worse primary disease control than surgery, but can be considered in patients who are not surgical candidates [42]. On the other hand, adjuvant radiotherapy plays a major role in the treatment of high-risk cSCCHN, including immunosuppressed patients [43]. Adjuvant radiation therapy is indicated for advanced-stage disease, perineural invasion, and significant nodal disease with or without extracapsular extension [41]. In general, adjuvant radiotherapy has been demonstrated to decrease the risk of failure in lesions at an increased risk for regional and distant metastasis. Perineural invasion is the most common reason to receive adjuvant radiotherapy. According to a recent systematic review, while patients with perineural invasion had a higher rate of locoregional failure, distant metastasis, and disease-specific death, there was no difference in outcome with the addition of adjuvant radiotherapy after surgery [43]. Close margins were also demonstrated to have a poorer prognosis, but the addition of adjuvant therapy again did not demonstrate a survival benefit. These results highlight the importance of adequate surgical clearance of disease before adjuvant radiation therapy.

Systemic Therapy

Because of the recurring nature of cSCCHN in immunosuppressed patients, systemic therapies have the greatest promise for patients with multifocal disease. Despite this, systemic therapy in cSCCHN, and particularly in those with immunosuppressed, is relatively unexplored. Small case series with cisplatin-based regimens have been completed in immunocompetent patients. Though overall response rates were promising, the duration of response was limited [44]. In the TROG 05.01 trial, the role of chemotherapy in the adjuvant setting was tested in 310 patients who were randomly assigned to receive radiotherapy alone vs. radiotherapy with weekly cisplatin. No difference in 2- or 5-year survival or recurrence outcomes was found [45]. Therefore, the role of cisplatin-based chemotherapy in cSCC continues to be controversial.

Targeted therapy, specifically epidermal growth factor receptor (EGFR) inhibitors, has also been investigated, but not in immunosuppressed patients. A phase II study on 26 immunocompetent patients with surgically unresectable cSCC was found to have a 69% disease control rate [46]. A phase I trial of 15 patients underwent treatment with erlotinib with radiotherapy demonstrated minimal toxicity with similar outcomes

to historical studies [47]. However, there has never been a head-to-head study comparing patients undergoing treatment with cisplatin-based vs. cetuximab [48•].

Most recently, immunotherapy has shown promise in patients with cSCCHN. A high tumor mutational burden has been demonstrated in patients with cSCC, and these patients appear particularly responsive to immunotherapy [49, 50]. A recent phase I and II clinical trial using cemiplimab, an anti-programmed death 1 (PD-1) human monoclonal antibody, in immunocompetent patients with surgically unresectable cSCC was completed [51••]. This study demonstrated a 47% response rate leading to United States Food and Drug Administration-approved use of cemiplimab for patients with cSCC who are not candidates for curative intent surgery or radiation therapy [52]. This study excluded immunosuppressed patients, and the role of immunotherapy in immunosuppressed patients remains less well defined. For solid transplant patients, a 41% acute graft rejection rate was observed in a review of immunosuppressed patients using immunotherapy for a variety of cancers [53•]. In patients with hematopoietic malignancies following stem cell transplantation and active autoimmune disease, there was an increased risk of toxicity with treatment with immunotherapy [53•]. On the other hand, in patients with HIV infections and stable cell counts, immunotherapy is felt to be a safe treatment option [53•]. In cSCC in particular, there has been reported one case of pembrolizumab use in a patient after renal transplant demonstrating a good tumor response but acute graft rejection [54•]. Thus, though immunotherapy demonstrates great promise in cSCC in immunocompetent patients, its utility in immunosuppressed patients still needs to be characterized. Studies are underway testing the local delivery of immunotherapy for cSCCHN. This novel approach could be particularly useful in immunosuppressed patients.

Neoadjuvant Therapy

As our understanding of systemic therapy improves, the role of neoadjuvant therapy continues to develop. With the increased aggressiveness of cSCCHN in immunosuppressed patients combined with the cosmetic and functional constraints of the head and neck, a neoadjuvant approach is attractive to facilitate subsequent definitive treatment and for risk stratification. A phase II study by Lewis et al. demonstrated a 45.5% overall response rate in 22 patients with cSCC using gefitinib prior to surgery or radiotherapy. Neoadjuvant treatment was generally well tolerated, with 88.2% of patients continuing to definitive treatment. Notably, this study demonstrated that markers for EGFR did not correlate to the level of response to treatment. As well, no immunosuppressed patients were included in this cohort.

With the promising findings of Migden et al.'s phase I and II trial, there has been much interest in immunotherapy in the neoadjuvant setting. A phase II clinical trial is currently underway, studying the use of cemiplimab prior to definitive treatment with surgery or radiation in patients with advanced cSCCHN [55]. While this study will not include immunosuppressed patients, understanding the role for immunotherapy as a neoadjuvant agent may potentially change treatment paradigms in these patients at risk for aggressive cSCC.

Conclusion

Immunosuppressed patients, including solid organ transplantation, hematologic malignancies, stem cell transplantation, autoimmune disease, and HIV, are at increased risk of cSCCHN. Immunosuppressed patients with cSCCHN have a worse prognosis with an increased risk of recurrence and death. While the treatment of cSCCHN in immunosuppressed patients remains primarily surgical, multidisciplinary care is critical given the aggressive nature of this disease. As such, novel preventative strategies and adjuvant treatment modalities such as radiation and systemic therapy are warranted. The evolving role of neoadjuvant strategies, targeted therapy, and immunotherapy requires further exploration in immunosuppressed patients with cSCCHN.

Compliance with Ethical Standards

Conflict of Interest Samantha Tam declares that she has no conflict of interest.

Neil D. Gross has served on a scientific advisory committee and has received research funding from Regeneron Pharmaceuticals, has served on an advisory committee for PDS Biotechnology, and has received honoraria from Intuitive Surgical.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kauvar AN, Arpey CJ, Hruza G, Olbricht SM, Bennett R, Mahmoud BH. Consensus for nonmelanoma skin cancer treatment, part II: squamous cell carcinoma, including a cost analysis of treatment methods. Dermatol Surg. 2015;41(11):1214–40.
2.•• Manyam BV, Garsa AA, Chin RI, et al. A multi-institutional comparison of outcomes of immunosuppressed and immunocompetent patients treated with surgery and radiation therapy for cutaneous squamous cell carcinoma of the head and neck. Cancer. 2017;123(11):2054–60. **Large, multiinstitutional cohort study of 205 patients with cutaneous squamous cell carcinoma of**

the head and neck undergoing surgery and radiation therapy direclty comparing 67 immunosuppressed vs. 138 nonimmunosuppressed patients. Locoregional and distant metastatic failure was higher in the immunosuppressed population (54% vs. 17%; 25% vs. 10%, respectively). Immunosupression was an independent preditor of locoregional failure (HR = 3.79).

3. Gray DT, Suman VJ, Su WP, Clay RP, Harmsen WS, Roenigk RK. Trends in the population-based incidence of squamous cell carcinoma of the skin first diagnosed between 1984 and 1992. Arch Dermatol. 1997;133(6):735–40.
4. Marrazzo G, Thorpe R, Condie D, Pinho MC, Srivastava D. Clinical and pathologic factors predictive of positive radiologic findings in high-risk cutaneous squamous cell carcinoma. Dermatol Surg. 2015;41(12):1405–10.
5. Pritchett EN, Doyle A, Shaver CM, Miller B, Abdelmalek M, Cusack CA, et al. Nonmelanoma skin cancer in nonwhite organ transplant recipients. JAMA Dermatol. 2016;152(12):1348–53.
6. Ulrich C, Arnold R, Frei U, Hetzer R, Neuhaus P, Stockfleth E. Skin changes following organ transplantation: an interdisciplinary challenge. Dtsch. 2014;111(11):188–94.
7. Imko-Walczuk B, Cegielska A, Placek W, Kaszewski S, Fiedor P. Human papillomavirus-related verrucous carcinoma in a renal transplant patient after long-term immunosuppression: a case report. Transplant Proc. 2014;46(8):2916–9.
8. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: incidence, risk factors, diagnosis, and staging. J Am Acad Dermatol. 2018;78(2):237–47.
9. Madeleine MM, Johnson LG, Daling JR, Schwartz SM, Carter JJ, Berg D, et al. Cohort profile: the skin cancer after organ transplant study. Int J Epidemiol. 2013;42(6):1669–77.
10. Koyfman SA, Cooper JS, Beitler JJ, Busse PM, Jones CU, McDonald MW, et al. ACR Appropriateness Criteria® aggressive nonmelanomatous skin cancer of the head and neck. Head Neck. 2016;38(2):175–82.
11. Mansh M, Binstock M, Williams K, Hafeez F, Kim J, Glidden D, et al. Voriconazole exposure and risk of cutaneous squamous cell carcinoma, aspergillus colonization, invasive aspergillosis and death in lung transplant recipients. Am J Transplant. 2016;16(1):262–70.
12. Wojenski DJ, Bartoo GT, Merten JA, Dierkhising RA, Barajas MR, el-Azhary RA, et al. Voriconazole exposure and the risk of cutaneous squamous cell carcinoma in allogeneic hematopoietic stem cell transplant patients. Transpl Infect Dis. 2015;17(2):250–8.
13. Brin L, Zubair AS, Brewer JD. Optimal management of skin cancer in immunosuppressed patients. Am J Clin Dermatol. 2014;15(4):339–56.
14. Robinson AA, Wang J, Vardanyan S, Madden EK, Hebroni F, Udd KA, et al. Risk of skin cancer in multiple myeloma patients: a retrospective cohort study. Eur J Haematol. 2016;97(5):439–44.
15. Velez NF, Karia PS, Vartanov AR, Davids MS, Brown JR, Schmults CD. Association of advanced leukemic stage and skin cancer tumor stage with poor skin cancer outcomes in patients with chronic lymphocytic leukemia. JAMA Dermatol. 2014;150(3):280–7.
16. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum. 2007;56(9):2886–95.
17. Amari W, Zeringue AL, McDonald JR, Caplan L, Eisen SA, Ranganathan P. Risk of non-melanoma skin cancer in a national cohort of veterans with rheumatoid arthritis. Rheumatology (Oxford, England). 2011;50(8):1431–9.
18. Asgari MM, Ray GT, Geier JL, Quesenberry CP. Malignancy rates in a large cohort of patients with systemically treated psoriasis in a managed care population. J Am Acad Dermatol. 2017;76(4):632–8.
19. Garritsen FM, van der Schaft J, van den Reek JM, et al. Risk of non-melanoma skin cancer in patients with atopic dermatitis treated with oral immunosuppressive drugs. Acta Derm Venereol. 2017;97(6):724–30.
20. Burgi A, Brodine S, Wegner S, Milazzo M, Wallace MR, Spooner K, et al. Incidence and risk factors for the occurrence of non-AIDS-defining cancers among human immunodeficiency virus-infected individuals. Cancer. 2005;104(7):1505–11.
21. Silverberg MJ, Leyden W, Warton EM, Quesenberry CP Jr, Engels EA, Asgari MM. HIV infection status, immunodeficiency, and the incidence of non-melanoma skin cancer. J Natl Cancer Inst. 2013;105(5):350–60.
22. Chen ST, Li T, Han J, Qureshi AA, Cho E. Type 2 diabetes mellitus and risk of cutaneous squamous cell carcinoma. J Am Acad Dermatol. 2016;75(4):831–4.
23. Manyam BV, Gastman B, Zhang AY, Reddy CA, Burkey BB, Scharpf J, et al. Inferior outcomes in immunosuppressed patients with high-risk cutaneous squamous cell carcinoma of the head and neck treated with surgery and radiation therapy. J Am Acad Dermatol. 2015;73(2):221–7.
24. Smith KJ, Hamza S, Skelton H. Histologic features in primary cutaneous squamous cell carcinomas in immunocompromised patients focusing on organ transplant patients. Dermatol Surg. 2004;30(4 Pt 2):634–41.
25. Varra V, Woody NM, Reddy C, et al. Suboptimal outcomes in cutaneous squamous cell cancer of the head and neck with nodal metastases. Anticancer Res. 2018;38(10):5825–30.
26.•• McLaughlin EJ, Miller L, Shin TM, et al. Rate of regional nodal metastases of cutaneous squamous cell carcinoma in the immunosuppressed patient. Am J Otolaryngol. 2017;38(3):325–8. **One of the largest reviews of 130 organ tranplant patients with cutaneous squamous cell carcinoma of the head and neck undergoing Mohs resection. There was a 1.8% per lesions regional metastatic rate or 5.4% per patient regional metastatic rate. All patients developing regional metastasis were using a calcineurin inhibitor.**
27. Bavinck JN, Tieben LM, Van der Woude FJ, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. J Clin Oncol : Off J Am Soc Clin Oncol. 1995;13(8):1933–8.
28. Euvrard S, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med. 2012;367(4):329–39.
29. Jirakulaporn T, Endrizzi B, Lindgren B, Mathew J, Lee PK, Dudek AZ. Capecitabine for skin cancer prevention in solid organ transplant recipients. Clin Transpl. 2011;25(4):541–8.
30. Ulrich C, Bichel J, Euvrard S, Guidi B, Proby CM, van de Kerkhof PCM, et al. Topical immunomodulation under systemic immunosuppression: results of a multicentre, randomized, placebo-controlled safety and efficacy study of imiquimod 5% cream for the treatment of actinic keratoses in kidney, heart, and liver transplant patients. Br J Dermatol. 2007;157(Suppl 2):25–31.
31. Ulrich C, Johannsen A, Rowert-Huber J, Ulrich M, Sterry W, Stockfleth E. Results of a randomized, placebo-controlled safety and efficacy study of topical diclofenac 3% gel in organ transplant patients with multiple actinic keratoses. Eur J Dermatol. 2010;20(4):482–8.
32. Willey A, Mehta S, Lee PK. Reduction in the incidence of squamous cell carcinoma in solid organ transplant recipients treated with cyclic photodynamic therapy. Dermatol Surg. 2010;36(5):652–8.
33. Surber C, Ulrich C, Hinrichs B, Stockfleth E. Photoprotection in immunocompetent and immunocompromised people. Br J Dermatol. 2012;167(Suppl 2):85–93.
34. Thomas BR, Barnabas A, Agarwal K, Aluvihare V, Suddle AR, Higgins EM, et al. Patient perception of skin-cancer prevention

and risk after liver transplantation. Clin Exp Dermatol. 2013;38(8):851–6.

35.• Funk-Debleds P, Ducroux E, Guillaud O, et al. Subsequent nonmelanoma skin cancers and impact of immunosuppression in liver transplant recipients. J Am Acad Dermatol. 2018;79(1):84–91. **Large retrospective study of liver transplant patients specifically comparing immunosuppression regimens and their effect on the invidence of cutaneous squamous cell carcinoma. Calcineurin inhibitor use was associated with an increased risk of a secondary skin cancer compared with withdrawal of calcineurin inhibitor for other immunosuppressive regimens.**

36. Moioli EK, Hsieh C, Tisch A, Bolotin D. Histologic status of squamous cell carcinoma in situ after diagnostic biopsy in immunocompetent and immunosuppressed patients. Dermatol Surg. 2018;44(3):341–9.

37. Basset-Seguin N, Baumann Conzett K, Gerritsen MJ, et al. Photodynamic therapy for actinic keratosis in organ transplant patients. J Eur Acad Dermatol Venereol : JEADV. 2013;27(1):57–66.

38. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Ingenol mebutate gel for actinic keratosis. N Engl J Med. 2012;366(11):1010–9.

39. Lebwohl M, Shumack S, Stein Gold L, Melgaard A, Larsson T, Tyring SK. Long-term follow-up study of ingenol mebutate gel for the treatment of actinic keratoses. JAMA Dermatol. 2013;149(6):666–70.

40. Mehrany K, Byrd DR, Roenigk RK, Weenig RH, Phillips PK, Nguyen TH, et al. Lymphocytic infiltrates and subclinical epithelial tumor extension in patients with chronic leukemia and solid-organ transplantation. Dermatol Surg. 2003;29(2):129–34.

41. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology - squamous cell skin cancer, version 2.2019. 2019; https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed March 28, 2019.

42. Jennings L, Schmults CD. Management of high-risk cutaneous squamous cell carcinoma. J Clin Aesthetic Dermatol. 2010;3(4):39–48.

43. Jambusaria-Pahlajani A, Miller CJ, Quon H, Smith N, Klein RQ, Schmults CD. Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous cell carcinoma: a systematic review of outcomes. Dermatol Surg. 2009;35(4):574–85.

44. Wells JL 3rd, Shirai K. Systemic therapy for squamous cell carcinoma of the skin in organ transplant recipients. Am J Clin Oncol. 2012;35(5):498–503.

45. Porceddu SV, Bressel M, Poulsen MG, Stoneley A, Veness MJ, Kenny LM, et al. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: the randomized phase III TROG 05.01 trial. J Clin Oncol : Off J Am Soc Clin Oncol. 2018;36(13):1275–83.

46. Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol : Off J Am Soc Clin Oncol. 2011;29(25):3419–26.

47. Heath CH, Deep NL, Nabell L, Carroll WR, Desmond R, Clemons L, et al. Phase 1 study of erlotinib plus radiation therapy in patients with advanced cutaneous squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2013;85(5):1275–81.

48.• Trodello C, Pepper JP, Wong M, Wysong A. Cisplatin and cetuximab treatment for metastatic cutaneous squamous cell carcinoma: a systematic review. Dermatol Surg. 2017;43(1):40–9. **Large systematic review of published cases comparing the role of cisplatin vs. cetuximab on patients with metastatic cutaneous squamous cell carcinoma involving 69 cases. This study found no head to head trials, but both demonstrated effectiveness in patients with cutaneous squamous cell carcinoma, but did not report on immunosuppression status.**

49. Pickering CR, Zhou JH, Lee JJ, Drummond JA, Peng SA, Saade RE, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. Clin Cancer Res: Off J Am Assoc Cancer Res. 2014;20(24):6582–92.

50. Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med. 2017;9(1):34.

51.•• Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med. 2018;379(4):341–51. **Phase I and II trial of 85 patients with locally advanced or metastatic cutaneous squamous cell carcinoma using cimiplimab (PD-1 inhibitor). This study was of immunocompetent patients only, with a 47% resopnse rate.**

52. U.S. Food & Drug Administration. FDA approves cemiplimab-rwlc for metastatic or locally advanced cutaneous squamous cell carcinoma. 2018; https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm622251.htm. Accessed March 28, 2019.

53.• Babey H, Quere G, Descourt R, et al. Immune-checkpoint inhibitors to treat cancers in specific immunocompromised populations: a critical review. Expert Rev Anticancer Ther. 2018;18(10):981–9. **A review of patients with immunosuppression undergoing immune-checkpoint inhibitors. Largest, most comprehensive study discussing the application of immunotherapy on patients with immunosuppression.**

54.• Lipson EJ, Bagnasco SM, Moore J Jr, et al. Tumor regression and allograft rejection after administration of anti-PD-1. N Engl J Med. 2016;374(9):896–8. **Case series of a patients with cutaneous squamous cell carcinioma and renal transplantation. Treatment with anti-PD-1 demosntrated significant tumor regression, but 2 months following initiation of treatment that patient's graft was acutely rejected.**

55. Cemiplimab in treating participants with recurrent stage III-IV head and neck squamous cell cancer before surgery (NCT03565783). https://ClinicalTrials.gov/show/NCT03565783.